Original Research Article

FORMULATION AND EVALUATION OF COLON SPECIFIC MELOXICAM MICROCAPSULES FOR THE TREATMENT OF ARTHRITIS

ABSTRACT

The primary goal of the current work was to use pH-dependent polymers to develop and evaluate meloxicam-loaded microcapsules for colon-specific medication delivery. The enolic acid non-steroidal inflammatory drug meloxicam is commonly prescribed for rheumatoid arthritis and osteoarthritis. Its poor and pH-dependent water solubility is one of its unique features. The main concern was the increasing demand to produce extended-release NSAIDs to try to minimise the frequency of dose. Hence, designing an oral extended-release formulation for arthritis treatment might be one method of avoid this problem with lesser side effects and improved adherence among patients.

Methods: Meloxicam (MLX) microcapsules were produced using Eudragit RS/RL-100 polymers in emulsion solvent evaporation methods. The developed MLX microcapsules had been tested to in vitro dissolution tests, yield, drug content, entrapment efficiency, compatibility tests (FTIR), and surface characteristics by Scanning Electron Microscopy (SEM).

Results: The IR spectra confirmed no interaction between the polymer and MLX. SEM revealed that the microcapsules were spherical. The resulting microcapsules ranged in size from 500 to 950 µm. MLX microcapsules with a normal frequency distribution were developed. 94% was the maximum drug entrapment efficiency that was achieved. The MLX microcapsules' in vitro performance revealed that sustained release had been controlled by the polymer concentration. In addition, the amount of polymer used has been shown to govern the drug's release.

Conclusion: The development of MLX microcapsules has been found to be the one of the most promising formulation methods for designing colon-specific drug delivery systems for treating arthritis.

Keywords: evaporation of emulsion solvent, arthritis, meloxicam, colon specific.

1. INTRODUCTION

The colon can be used as a modified release technique as its pH exceeds than compared to that of the rest of the gastrointestinal tract (GIT). Eudragit polymer, which could provide both pH-dependent release and mucoadhesiveness, is the most frequently utilised synthetic material utilised for the development of colonic release formulations. Colonic delivery systems are composed of both pH-dependent and permeable polymers that break down at a pH range of 6.0–7.0 to prolong the release of the medication before it goes into the colon or pH-independent and low permeability polymers.[1] By preventing drug release and absorption in

the target drug delivery's stomach and small intestine, as well as by blocking the bioactive ingredient from breakdown in either of the dissolution sites, the colon specific drug delivery system (CDDS) protects the drug from being delivered to the colon. The ability of the Gut to absorb drugs orally is extremely restricted, whereas CDDS is required for protecting the body from the severe conditions of the upper GIT.[2] A combination of one or more controlled release mechanisms is utilized for targeted drug delivery to the colon; the drug is consumed orally and releases rapidly in the colon but does not dissolve in the upper region of the GIT. Delivering the drug selectively to the colon would have several advantages, like higher safety and lower toxicity, for treating local or systemic persistent illnesses.[3] For colonic drug administration to be successful, several variables need to be taken into consideration, like the drug's characteristics, the type of method of administration, and how the drug interacts with a healthy or sick gut. For example, whether a systemic or local effect is needed, the drug must first dissolve in the luminal contents of the colon. [4] Most conventional drug delivery methods for colon diseases are failing since drugs are unable to reach to the site of action in appropriate quantities.

The enolic acid group of oxicam derivatives can be represented by 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2- benzothiazine-3-carboxamide 1,1-dioxide, which is also known as meloxicam (MLX). The BCS classification approach classifies MLX in class-II according to its solubility and permeability properties.[5] In spite of exhibiting an elimination half-life of almost 20 hours, it has inadequate water solubility and a low dissolution rate (4.4 µg/mL at water). It is frequently utilised to manage acute pain, stiffness, and inflammation produced on by ankylosing spondylitis and rheumatoid arthritis. tendon inflammation, osteoarthritis, and injuries. The therapeutic efficacy of MLX is limited by its insufficient solubility, resulting in poor absorption and dissolution from the gastrointestinal tract (GIT) at physiologic pH. [6] Dyspepsia, ulceration, pain in the stomach, and bleeding are a few of the gastrointestinal side effects of MLX that severely restrict its clinical efficacy and may also limit the duration of its use for the prevention of colon cancer. Thus, it is necessary to develop an appropriate drug carrier system for the controlled and efficient management of MLX to the colonic region.

Due to its reduced solubility, resulting in poor dissolution and limited absorption from the gastrointestinal tract (GIT) at physiologic pH, MLX's therapeutic efficacy is limited. Bleeding, ulceration, dyspepsia, and discomfort in the stomach are some of the digestive side effects of MLX that significantly limits its use for therapy and can even prevent long-term use. For MLX to be delivered to the colonic area in a regulated efficient way, an appropriate drug carrier technique has to be designed. [7, 8]

For the most effective potential delivery of the drugs at the site of action after oral administration, drug release control is important. The adverse effects of conventional dose forms can be minimised via a controlled release delivery system, that may maintain a constant plasma drug concentration for an extended duration. Unfortunately, it can be difficult to identify the site of action due to poor drug solubility, degradation, limited bioavailability, and bio-distribution. An approach of dealing this low solubility and low bioavailability is to encapsulate the drugs in a polymeric matrix which allows precise and controlled drug release at a consistent rate for a longer period of duration. [9–13]

Recently, there has been an increase of interest in the numerous and flexible features of polymeric

particulate systems, including microparticles, nanoparticles, and microsponges. In the meantime, to overcome issues with low solubility, restricted bioavailability, and drug degradation, as well as to control-controlled release distribution at the site of action, microparticles and nanoparticles are often produced from biocompatible and biodegradable polymers.

Microparticles with diameters between 1 and 1000 µm are spherical particles with a polymeric coating that usually governs drug release from the microparticles and an active pharmacological ingredient in the core. It can be produced through a number of methods such as solvent evaporation, fluidised bed, conservation, spray drying, and interfacial polymerisation. The oil in oil (O/O) emulsion solvent evaporation (ESE) method was employed to produce the microparticles in the present research because it is simple to produce, does not require serious processing conditions, and does not impact drug activity. It mainly serves to microencapsulate drugs with low aqueous solubility that dissolve in the dispersion phase. [14–18]

There are several justifications how microencapsulation is used: (i) to safeguard sensitive materials from the surroundings; (ii) to hide the material's organoleptic characteristics (colour, taste, and smell); (iii) to attain controlled drug release; (iv) to make certain which hazardous materials are dealt with securely; (v) to attain targeted drug release; and (vi) for minimising unwanted side effects like gastric irritation (the first medication used to prevent gastric irritation is aspirin) Therefore, the goal of the present research was to utilise pH-dependent polymers to develop and assess meloxicam-loaded microcapsules for colon-specific drug delivery.

2. MATERIALS AND METHODS

2.1. Materials

Meloxicam was received as a gift sample from Zydus Lifesciences Ltd, Ahmedabad. The Eudragit RL-100 and RS-100 are obtained from Evonik Industries, Mumbai. Acetone, Span 80, Light liquid paraffin and Heavy liquid paraffin from Karnataka fine chem. Ltd, Bangalore. The other solvents and reagents used were of analytical grade.

2.2. Compatibility Studies

Compatibility of the MLX with polymers viz. Eudragit RL/RS 100, and physical mixture of the main formulation was established by infrared absorption spectral analysis (IR). Any changes in chemical composition of the drug after combining it with the excipients were investigated with I.R. spectral analysis. In the present study, the potassium bromide disc (pellet) method was employed.

2.3. Preparation of microcapsules of MLX

Emulsification-solvent evaporation method

To produce a consistent polymer solution, Eudragit RL-100 and RS-100, each of which was precisely weighed, were dissolved in 10 ml of acetone. MLX, the core material, was added to the polymer solution and it was thoroughly mixed. To formulate a smooth emulsion, this organic phase was slowly mixed with 150 ml of liquid paraffin containing 1% w/w of Span-80 at 15ºC while it was stirring at 1200 rpm. After this, it was allowed to attain room temperature after being continuously stirred until any residual acetone evaporated and separate, hard, and smooth-walled microcapsules formed. After collecting the microcapsules by decantation,

the final product was washed four times with petroleum ether (40–60°C) and allowed to dry for three hours at room temperature.

The microcapsules were subsequently kept over fused calcium chloride in a desiccator. Different ratios of core to coat materials were used to make six batches, numbered F-1 to F-6, where the drug with polymers Eudragit RL/RS 100 is present in F-1 and F-2, the drug with Eudragit RL100 is present in F-3 and F-4, and the drug with Eudragit RS100 is present in F-5 and F-6 (Table 1).

Table 1 Formulation Design of MLX Microcapsules.

Sl No	Ingredients	Formulation code					
		F1	F2	F3	F4	F5	F6
1	Drug(mg)	1000	1000	1000	1000	1000	1000
2	Eudragit RL-100 (mg)	300	500	300	500	-	-
3	Eudragit RS-100 (mg)	300	500	-	-	300	500
4	Span-80 (ml)	0.5	0.5	0.5	0.5	0.5	0.5
5	Acetone (ml)	10	10	10	10	10	10

2.4. Evaluation of microcapsules

2.4.1. Particle size and Surface morphology

Using optical microscopy and a stage micrometre, the mean particle size of MLX microcapsules has been determined. A small quantity of microcapsules have been placed on a clean glass slide, and each batch's average size of 300 microcapsules was determined. Scanning electron microscopy was used to determine surface topography, texture, and the morphology of microcapsules. SEM is possibly the most commonly used technology to analyse drug delivery systems because it is simple to use and preparing samples is easy. The JEOL JSM T-330 Scanning Microscope was used to carry out the studies. Dry microcapsules were coated with gold by using an ion sputter and set on a brass stub for an electron microscope. Microcapsule images were obtained by randomly scanning the stub.

2.4.2. Frequency distribution analysis

To assist in identifying a frequency distribution or compare the properties of particles with a wide range of sizes, the frequency distribution can be divided into various size ranges and displayed as a histogram. The percentage of particles with a certain equivalent diameter can be ascertained using the histogram, which also provides an interpretation of the frequency distribution.

2.4.3. % Yield and Drug entrapment efficiency

The percent yield of each of the sample was calculated from the expression:

$$\% \text{ Yield} = \frac{weight\ of\ micro\ particles}{weight\ of\ solid\ starting\ materials} \text{ X } 100$$

- **Determination of percentage drug entrapment efficiency (PDE)**

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment as per the following formula

$$PDE = \frac{Practical\ drug\ content}{theoretical\ drug\ content} X\ 100$$

- **Drug content:**

25 mg of crushed microcapsules were added to a 100 ml volumetric flask, and the volume was adjusted to a pH 7.4 mark. An orbital shaker incubator was used to shake the flask for 12 hours. After filtering the solution, the filtrate was used to make appropriate dilutions, and the absorbance at 362 nm was measured.

2.4.5. *In- vitro* dissolution Studies

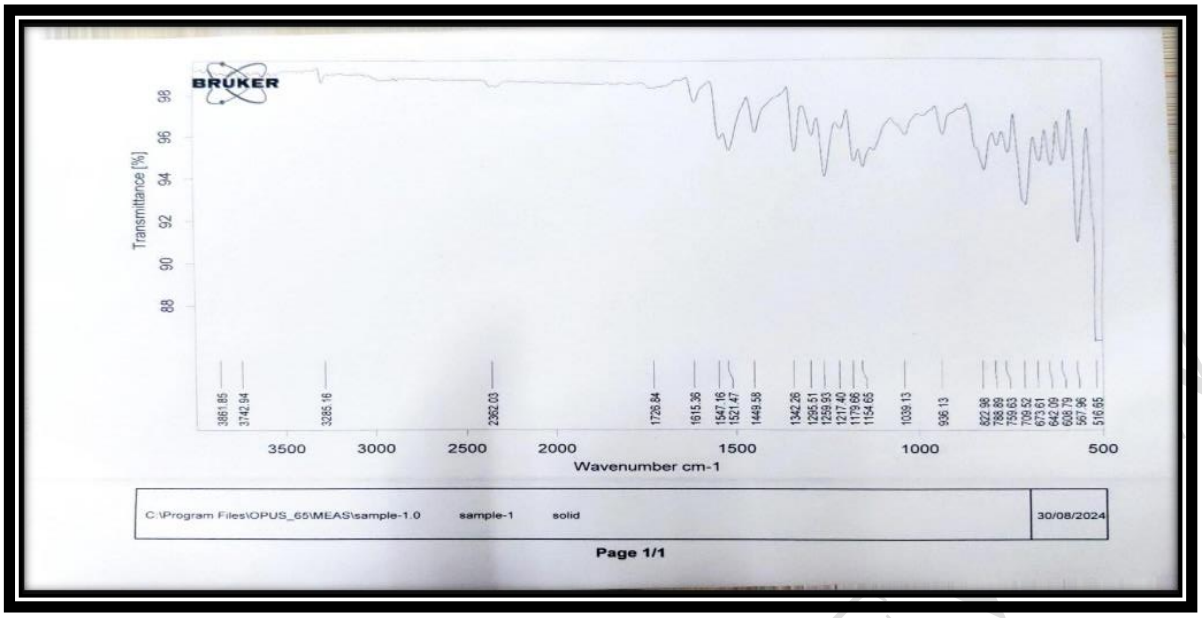
Using the USP XXIII rotating basket method (900 ml pH 1.2, pH 6.8, and pH 7.4 phosphate buffer, 100 rpm, 37º±0.5ºC), the in-vitro dissolution profile of each formulation was ascertained. The dissolution apparatus's basket was filled with MLX microcapsules. At appropriate intervals, 5 ml of the sample was taken out of the dissolution media, and the same volume was added to new buffer. The filtrate's absorbance was measured against a blank at a wavelength of 362 nm. The calibration curve was then used to determine the amount of drug contained in the filtrate, and the cumulative percent of drug release was determined.

3. RESULTS AND DISCUSSION

The goal of the current study was to create and assess Eudragit microcapsules of MLX for colon-specific management and enhanced arthritis treatment. MLX used colonically may avoid unwanted systemic side effects.

3.1. Compatibility study by IR Spectroscopy [19]

To check for any potential interactions between the drug and the polymers, a compatibility study was carried out. All of the individual peaks of MLX were found in the combination spectrum, indicating the compatibility of MLX and polymers, as illustrated in Figure 1, based on the spectra of MLX, the physical mixing of MLX and polymers, and MLX microcapsules. According to the IR investigations, there is no issue with drug-polymer incompatibility.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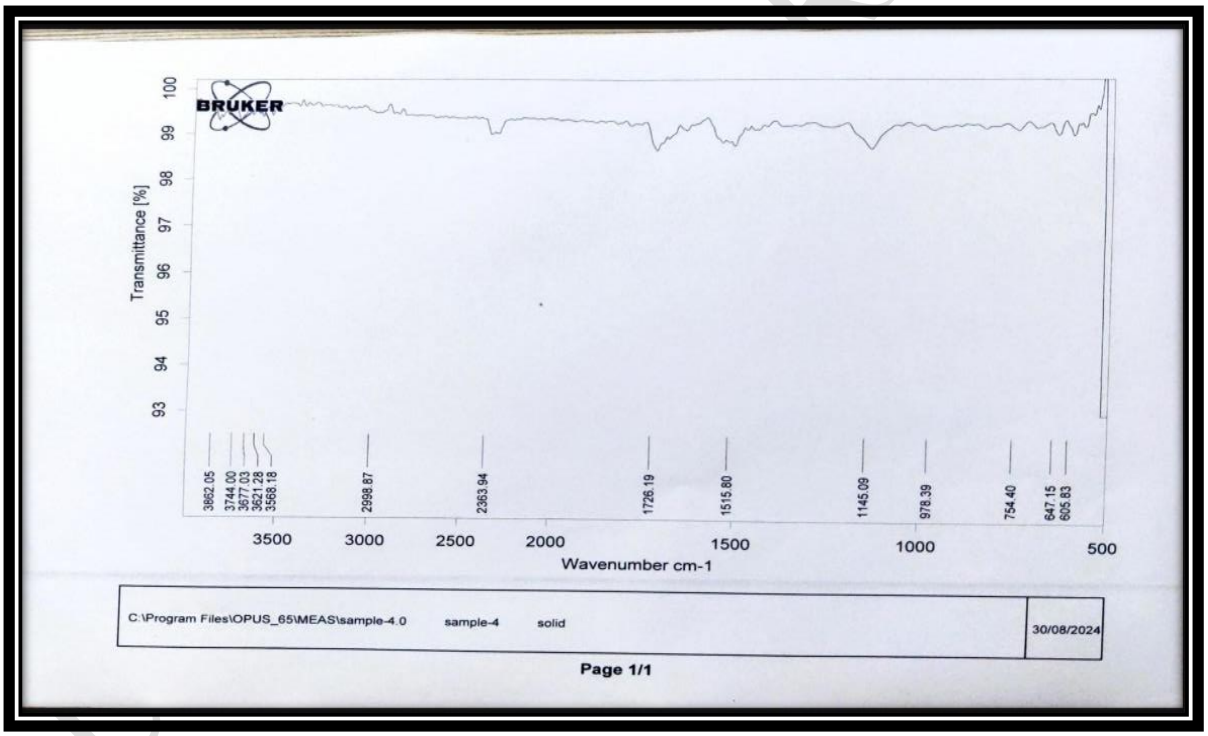
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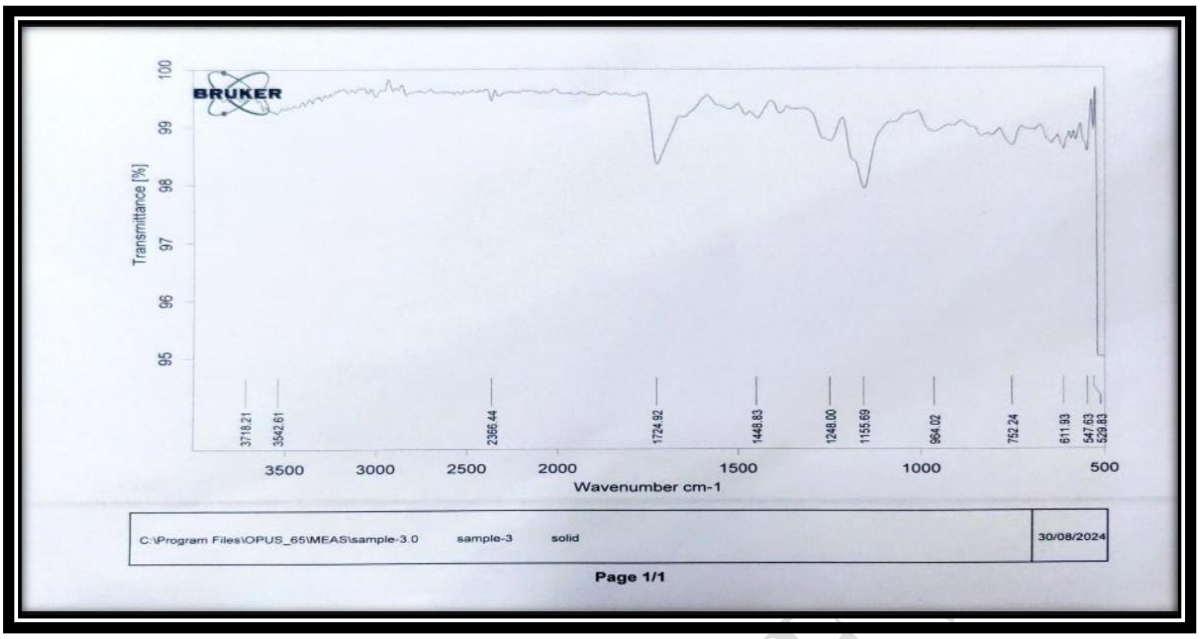

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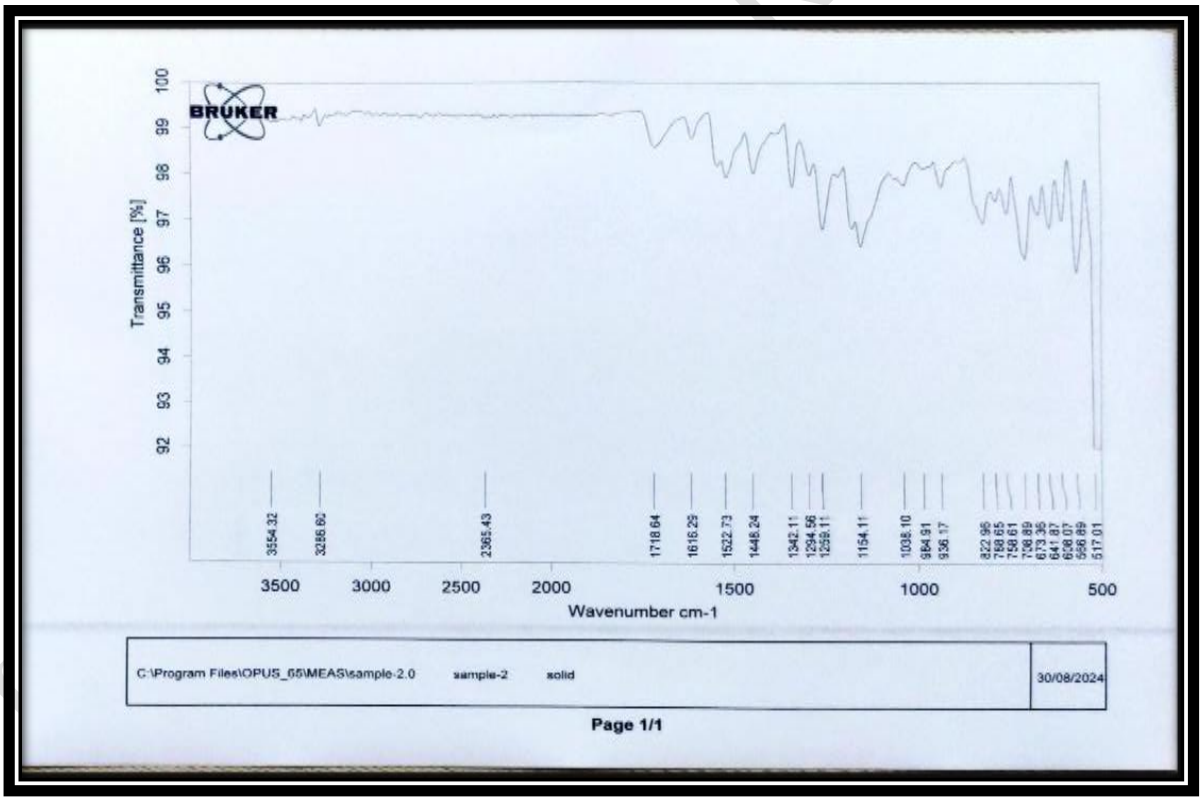
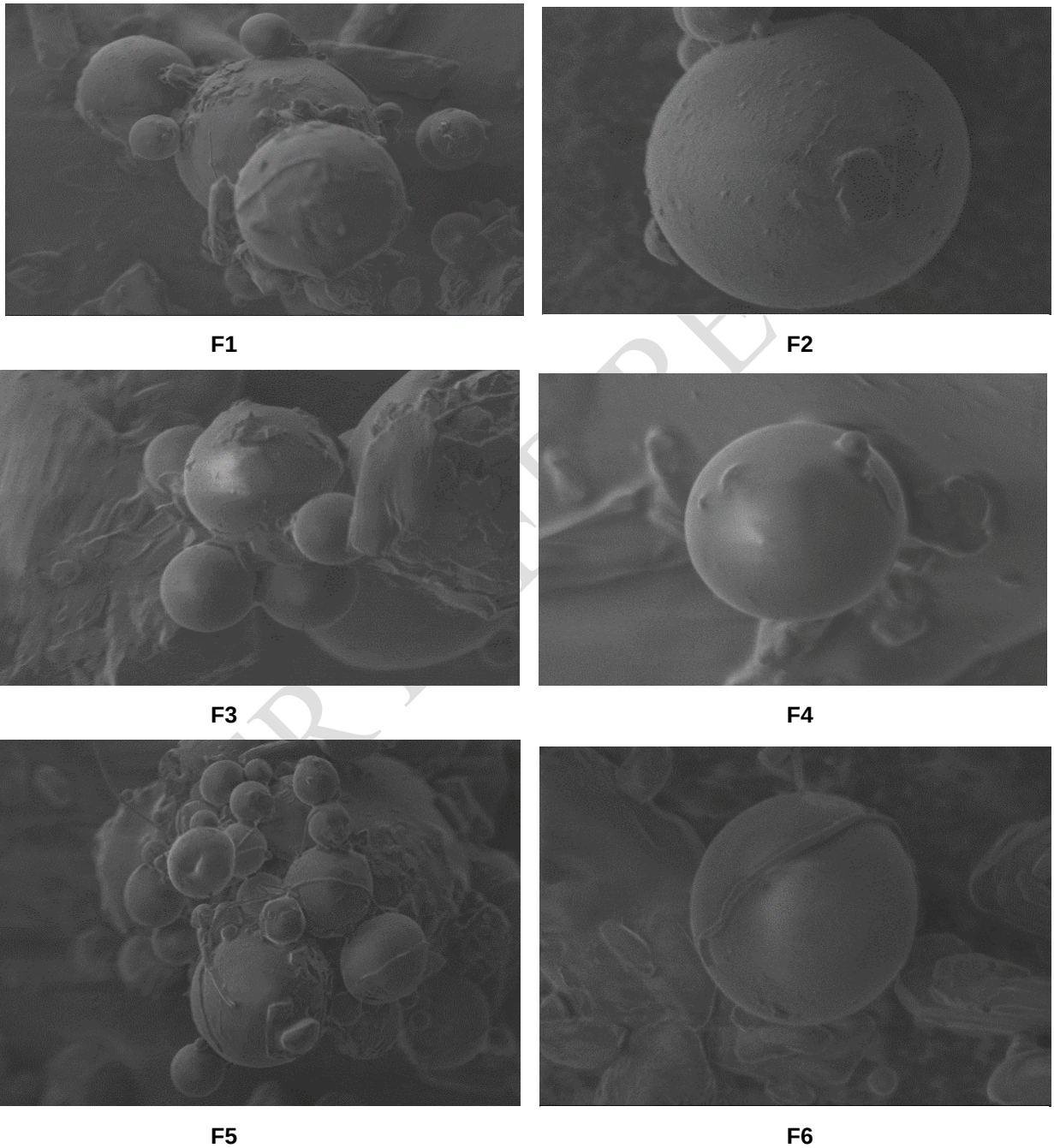


(D)

Fig 1: IR Spectrum of (A) MLX, (B) physical mixture of MLX, Eudragit RL100, (C) physical mixture of MLX, Eudragit RS100 and (D) MLX microcapsules of Eudragit RL/RS100

3.2. Scanning Electron Microscopy (SEM)

The surface of the produced microcapsules was studied using scanning electron microscopy. It is found that particles are smooth, round, and distinct. Figure 2 shows scanning electron photomicrographs of each of the six formulations. By increasing the polymer concentration, MLX microcapsules' surface smoothness is enhanced. [19]



F1 **F2**

F3 **F4**

F5 **F6**

Fig 2: SEM Photography of MLX microcapsules of F1-F6

3.3. Determination of average particle size [20]

The optical microscope, which was equipped with an ocular micrometre and a stage micrometre, was used to calculate the formulations' arithmetic mean size. According to Table 2 and Figure 3, the average mean particle sizes of the microcapsules for formulations F-1, F-2, F-3, F-4, F-5, and F-6 were 628,708, 798, 839,782, and 870 µm, respectively.

The microcapsules' mean particle size, which ranged from 628 to 870 µm, grew noticeably as the polymer content rose. The reason must be that increased interfacial tension is caused by the medium's increased viscosity at greater polymer concentrations. Higher viscosities can reduce shearing efficiency. Larger particles might be forming as a result of this. The notable rise could be attributed to the droplets' increased viscosity, which could be brought on by the polymer solution's rising concentration.

Table 2: Average Diameter of MLX Microcapsules

Sl no	Formulation code	Average size (µm)
1	F 1	628 ± 2.73
2	F 2	708 ± 6.53
3	F 3	798 ± 3.83
4	F 4	839 ± 7.06
5	F 5	782 ± 4.02
6	F 6	870 ± 7.00

SD= Standard Deviation (n=3)

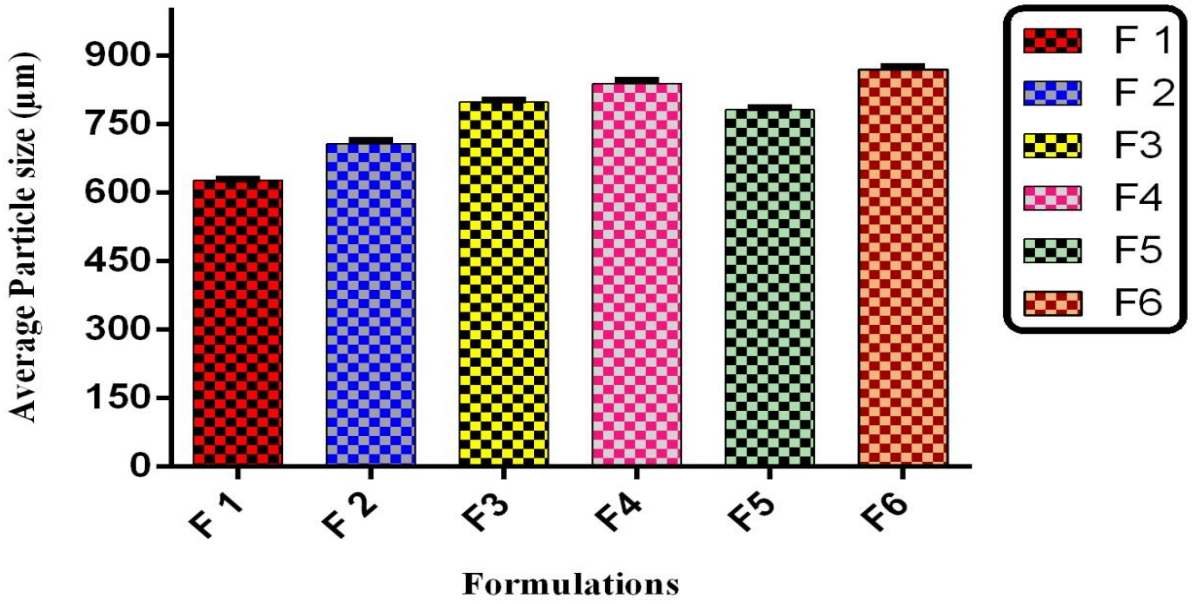


Fig 3: Average Diameter of MLX microcapsules

3.4. Frequency distribution analysis

Microcapsules have a normal frequency distribution, according to the results of frequency distribution studies and histograms (Table 3 and Fig 4). As indicated in Table 4, the average particle yield for each formulation was higher. The percentage yield and solid content were shown to be positively correlated. This may be explained by the fact that, even though a fixed amount of material is always lost during processing, the loss is proportionately less significant the higher the solid content (for example, if the processing loss is 10 mg, it is more significant for a sample of 100 mg but much less significant for a sample of 500 mg). [18]

Table 3: Frequency Distribution data of MLX microcapsules

Size range	Number of particles					
µm	F 1	F 2	F 3	F 4	F 5	F 6
500-550	15	5				
550-600	25	25	15	14		
600-650	25	30	45	30	25	20
650-700	40	40	60	45	60	40
700-750	90	50	95	70	90	85
750-800	65	85	35	65	75	95
800-850	45	65	25	55	50	35
850-900			20	21		25
900-950			5			

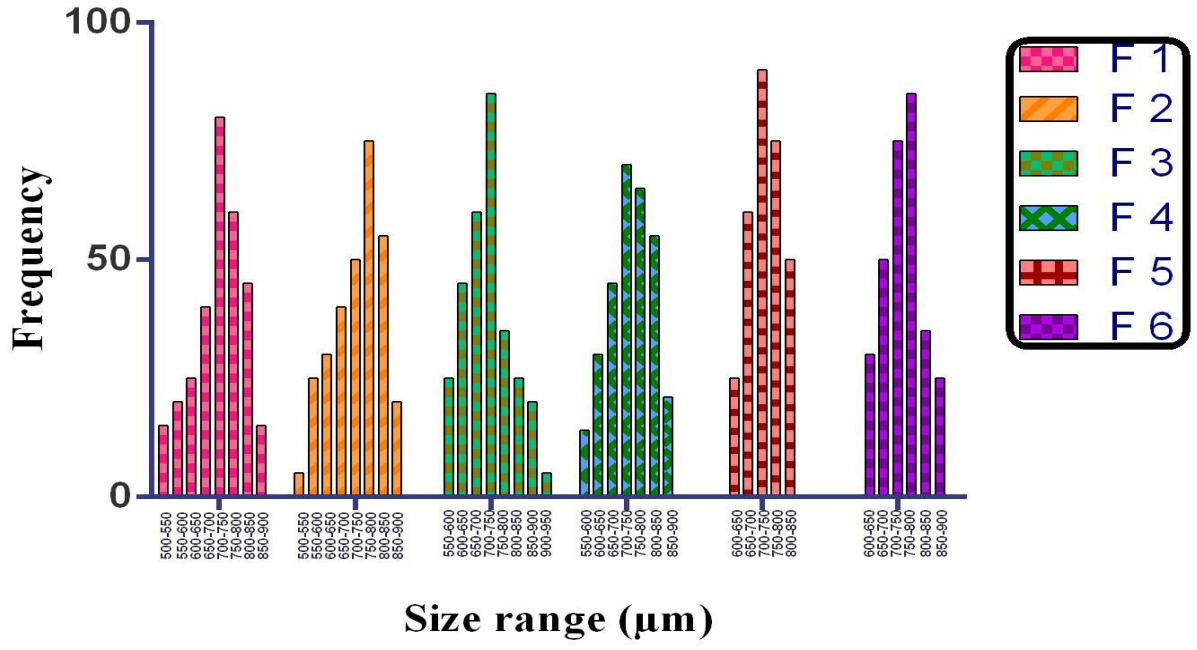


Fig 4: Frequency Distribution of MLX microcapsules

3.5. Drug entrapment efficiency [21]

As the concentration of the polymer increases, correspondingly increases the entrapment efficiency. Based on the results, it can be concluded that the microcapsules have a suitable MLX distribution and that the deviation is within the allowed limits. The drug content percentage was discovered to be between 20.42% and 82.32%. It was discovered that the trapping efficiency ranged from 26.00% to 94.50%. The outcome is shown in Fig. 5 and Table 4. The MLX microcapsules had a maximum drug entrapment efficiency of 94.50%, 86.20%, and 73%. In the MLX microcapsules, the drug entrapment efficiency was determined to be F2 > F1, F4 > F3, and F6 > F5ed. The order of drug entrapment efficiency was found to be F2 >F1, F4>F3 and F6>F5.

Table 4: Drug entrapment efficiency of MLX microcapsules

Formulation	% Yield	% Drug Content	Entrapment Efficiency (%)
F1	76.49	69.82	56.60 ± 1.50
F2	96.99	82.32	94.50 ± 1.09
F3	79.10	47.99	67.00 ± 3.50
F4	90.40	70.02	86.20 ± 4.07
F5	50.91	20.42	26.00 ± 2.30
F6	83.86	69.88	73.00 ± 1.05

SD= Standard Deviation (n=3)

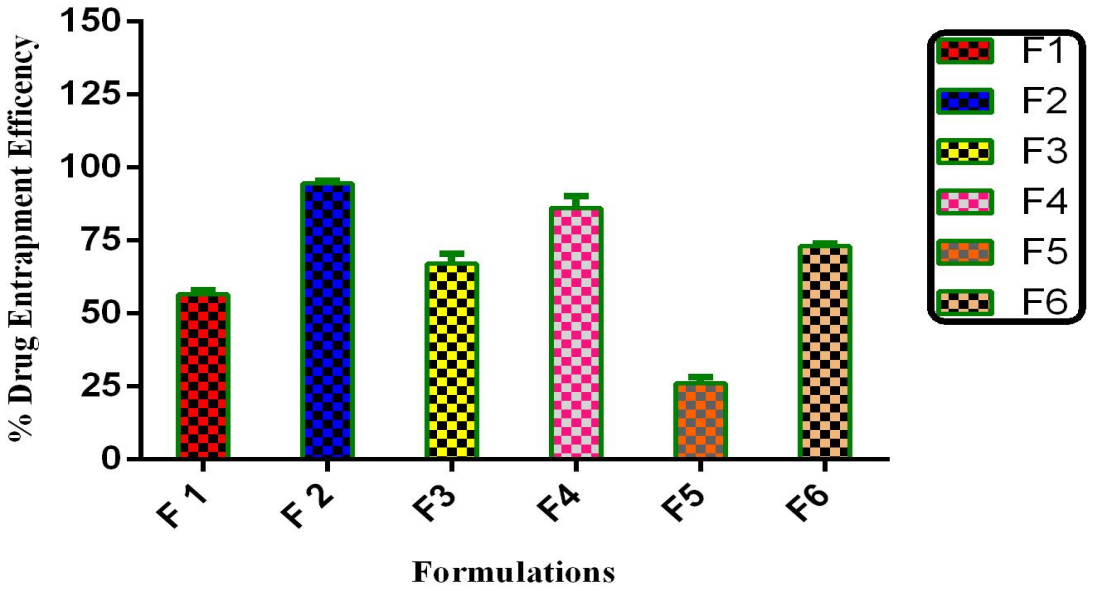


Fig 5: Drug entrapment efficiency of MLX microcapsules

3.6. *In-vitro* release studies of MLX microcapsules [22]

It was observed that the drug release from the formulations decreased with an increase in the amount of polymer added in each formulation. Drug releases for F1 to F6 were 8.03%, 7.25%, 14.32%, 11.46%, 16.09%,

and 13.14% in the first hour, respectively. The drug loaded on the microcapsules or the drug's poor entrapment may be the cause of the burst release mechanism. At the end of the tenth hour, the cumulative percentage release for F1, F2, F3, F4, F5, and F6 was 94.92%, 81.84%, 90.34%, 84.43%, 89.85%, and 86.34%, respectively (Fig 6).

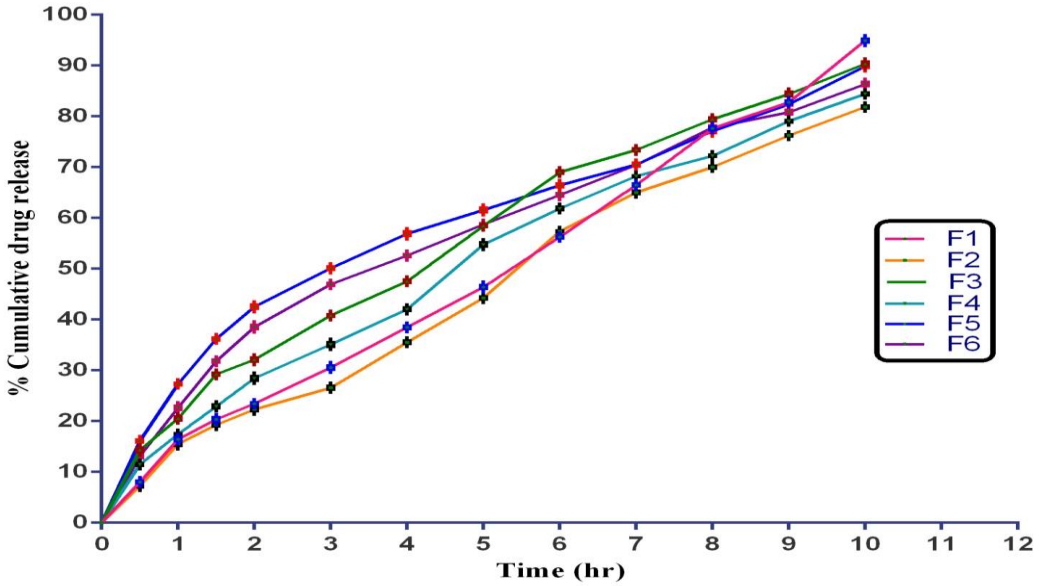


Fig 6: *Invitro* release profile of MLX microcapsules

4. CONCLUSION

The IR spectra in the Preformulation study reveal that MLX and polymers did not interact. The MLX was compatible with every polymer that was utilised. Microcapsules for colonic targeting can be prepared using Eudragit RL-100 and RS-100 in a 1:2 ratio. It is discovered that particles are smooth, round, and distinct. SEM confirmed that increasing the polymer concentration improved the MLX microcapsules' surface smoothness. The mean particle size of MLX microcapsules grew in tandem with an increase in the drug to polymer ratio. Normal frequency distribution MLX microcapsules were produced. Based on the results, it can be concluded that MLX was distributed correctly within the microcapsules and that the deviation was within allowable bounds. Entrapment efficiency also rises as the concentration of polymer increases. The dissolution investigation also showed that when the concentration of the polymer increases, the amount of medication release reduces. MLX microcapsules demonstrated long-lasting, sustained drug release in vitro. All microcapsules with an initial burst release action exhibited a biphasic release pattern during in vitro drug release, which may be explained by the drug being loaded onto the particle surface. In order to deliver colon-specific drug delivery systems for the treatment of arthritis with fewer side effects and better patient compliance, the created MLX microcapsules can therefore be regarded as one of the most promising formulation strategies.

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